**Treatment Options for Obesity And Potential Therapies on the Horizon**

Carol A. Motycka, PharmD; Erin St. Onge, PharmD; and Shannon A. Miller, PharmD

**INTRODUCTION**

The terms overweight and obesity refer to a person’s weight when it is higher than what is usually considered desirable and healthy relative to the person’s height. To determine whether an individual is overweight or obese, the body mass index (BMI) is used. BMI is calculated by taking one’s weight in pounds and multiplying it by 703. That number is then divided by the height in inches squared, as follows:

\[
\text{BMI} = \frac{\text{weight (lb.) \times 703}}{\text{height (in.)}^2}
\]

According to the Centers for Disease Control and Prevention (CDC), an adult is considered to be overweight if the BMI falls between 25 and 29.9 kg/m² and obese if the BMI is 30 or greater (Table 1).²

Overweight and obesity are caused, in part, by an energy imbalance in which calorie consumption exceeds calorie expenditure. However, it is now understood that genetics, metabolism, behavior, environment, cultural background, and socioeconomic status play a role as well (Figure 1).³

Although one report showed that the prevalence of obesity in the U.S. did not increase between 2007 and 2008 at the same rate as in previous years, the incidence of obesity remains high. In fact, approximately 32% of adult men and 36% of adult women are considered to be obese.⁴ In 1998, 9.1% of the national health care expenditure ($78.5 billion) in the U.S. was attributed to the direct medical costs of obesity. Indirect medical costs, such as lost productivity, totaled $47.6 billion.⁵

Following a brief review of traditional agents used for the treatment of obesity, we will discuss therapies that are in various stages of development (Table 2).

**ANTI-OBESEITY MEDICATIONS**

Behavioral and lifestyle modifications continue to be the cornerstone of obesity treatment. Unfortunately, these modifications are often met with limited long-term success; in such cases, pharmacological therapy may be indicated (Table 3).²

**Orlistat (Xenical, Alli)**

Orlistat (Xenical, Roche) is one of only two medications approved by the FDA for the treatment of obesity. A lipase inhibitor, it prevents the breakdown of dietary triglycerides to fatty acids and monoglycerides. The prescribed dose of 120 mg three times daily is taken with meals and prevents approximately 30% of ingested fat from being absorbed.⁶ According to a meta-analysis published in 2005, orlistat is associated with a mean weight loss of 2.6 kg at six months and a mean loss of 2.9 kg at 12 months, after the weight loss observed in the control group is subtracted.⁷ However, adverse effects (AEs), including flatulence, steatorrhea, increased stool frequency, fecal incontinence, and oily fecal discharge, limit the use of orlistat.⁵ This agent can also cause decreased absorption of the fat-soluble vitamins A, D, E, and K. Patients should thus be encouraged to take a supplement containing these vitamins two hours before each orlistat dose.⁶

Orlistat is also available over the counter as Alli (Glaxo-SmithKline) at a 60-mg dose.

**Table 1  Weight Classification According To Body Mass Index (BMI)**

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5–24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25–29.9</td>
</tr>
<tr>
<td>Obese Class I</td>
<td>30–34.9</td>
</tr>
<tr>
<td>Obese Class II</td>
<td>35–39.9</td>
</tr>
<tr>
<td>Obese Class III</td>
<td>≥40</td>
</tr>
</tbody>
</table>


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**Disclosure:** The authors report no commercial or financial relationships in regard to this article.
Sibutramine (Meridia)

Sibutramine (Meridia, Abbott) inhibits serotonin and noradrenaline reuptake and increases satiety. The prescribed dose is 10 to 15 mg once daily. A meta-analysis published in 2004 reported an average weight loss of 4.5 kg at one year.

Common AEs have included headache, insomnia, dry mouth, and constipation. Because sibutramine has been reported to increase blood pressure and heart rate, its use in cardiac patients should be closely monitored or avoided.

In October 2010, an expert panel of the FDA recommended either restricting prescribing sibutramine or withdrawing it, and the manufacturer decided to withdraw the drug from the market. These recommendations were made following the release of data from the Sibutramine Cardiovascular Outcomes (SCOUT) trial.

In this randomized, double-blind, placebo-controlled study, cardiovascular events were measured in patients taking sibutramine or placebo. The study enrolled 10,744 overweight or obese subjects, 55 years of age or older, with pre-existing cardiovascular disease, type-2 diabetes mellitus, or both. All patients received sibutramine during a lead-in period and achieved a placebo-subtracted weight loss of 2.6 kg. Six weeks later, subjects received either sibutramine (n = 4,906) or placebo (n = 4,898); the mean duration of treatment was 3.4 years. After randomization, the sibutramine group achieved and maintained an additional placebo-subtracted weight loss of 1.7 kg.

The main concern arose from the rates of the primary outcome events, including nonfatal myocardial infarction (MI), nonfatal stroke, resuscitation after cardiac arrest, and cardiovascular death. The sibutramine group had an 11.4% rate of primary outcome events, compared with 10% for the placebo group (P = 0.02). The rates of nonfatal MI were 4.1% with sibutramine and 3.2% with placebo (P = 0.02). Nonfatal stroke rates were 2.6% with the study drug and 1.9% with placebo (P = 0.03). Rates of cardiovascular death and all-cause mortality were the same in both groups.

Phentermine (Ionamin, Adipex-P)

Phentermine decreases the desire for food and may increase metabolism by stimulating the release of norepinephrine. Two forms of phentermine are available, phentermine resin (Ionamin, UCB Pharma) and phentermine HCl (Adipex-P, Gate). The prescribed resin dose is 15 to 30 mg daily, and the HCl dose is 18.75 to 37.5 mg daily. Phentermine is a controlled substance and has been approved by the FDA for use up to three months.

Commonly reported AEs include headache, insomnia, irritability, palpitations, and nervousness. Phentermine has also

Table 2 Single-Entity Medications for the Treatment of Obesity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Approval Status</th>
<th>Dose</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat (Xenical, Alli)</td>
<td>Lipase inhibitor</td>
<td>FDA-approved</td>
<td>120 mg t.i.d. (prescription product, Xenical) 60 mg t.i.d. (over-the-counter product, Alli)</td>
<td>Flatulence, steatorrhea, increased stool frequency, fecal incontinence, oily fecal discharge; kidney damage</td>
</tr>
<tr>
<td>Sibutramine (Meridia)</td>
<td>5-HT and NE reuptake inhibitor</td>
<td>Withdrawn in October 2010</td>
<td>10–15 mg daily</td>
<td>Headache, insomnia, dry mouth, constipation</td>
</tr>
<tr>
<td>Phentermine (Adipex-P, Ionamin)</td>
<td>Stimulates NE release</td>
<td>FDA-approved for short-term use only</td>
<td>18.75–37.5 mg daily (HCl product, Adipex-P) 15–30 mg daily (resin product, Ionamin)</td>
<td>Headache, insomnia, irritability, palpitations, nervousness</td>
</tr>
<tr>
<td>Liraglutide (Victoza)</td>
<td>GLP-1 receptor analog</td>
<td>Approved for type-2 diabetes mellitus; off-label use for weight loss</td>
<td>Undetermined</td>
<td>Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Lorcaserin (Lorqess, APD-356)</td>
<td>Selective 5-HT2 agonist</td>
<td>FDA denied NDA in October 2010</td>
<td>10 mg b.i.d. (expected dose)</td>
<td>Headache, upper respiratory infection, nausea, nasopharyngitis, dizziness</td>
</tr>
<tr>
<td>Tesofensine (NS-2330)</td>
<td>5-HT, NE, and DA inhibitor</td>
<td>Phase 2</td>
<td>Undetermined</td>
<td>Nausea, constipation, dry mouth</td>
</tr>
<tr>
<td>Cetilistat (ATL-962)</td>
<td>GI and pancreatic lipase inhibitor</td>
<td>Phase 3</td>
<td>Undetermined</td>
<td>Flatulence, steatorrhea, increased stool frequency, fecal incontinence, oily fecal discharge</td>
</tr>
</tbody>
</table>

b.i.d. = twice daily; DA = dopamine; GI = gastrointestinal; GLP = glycoprotein; 5-HT = hydroxytryptamine (serotonin); NDA = New Drug Application; NE = norepinephrine; t.i.d. = three times daily.
be associated with increases in heart rate and blood pressure; therefore, patients at risk of cardiac complications should be monitored closely.6

Phentermine is available in a generic formulation, which is a cost advantage.

NOVEL OBESITY TREATMENTS

Rimonabant (Acomplia)

In light of the fact that marijuana increases appetite, it had been postulated that by antagonizing the receptors that marijuana stimulates, cannabinoid receptor subtype 1 (CB1), the opposite effect might occur—suppression of appetite.13 Sanofi-Aventis was the first company to begin working on a compound, rimonabant (Acomplia, Sanofi-Aventis), the initial drug studied in the class of CB1 antagonists. Promising results were noted in the Rimonabant in Obesity (RIO) trials, which confirmed a consistent decrease in body weight over placebo as well as statistically significant improvements in other cardiovascular risks factors, such as decreased glycosylated hemoglobin (HbA1c), decreased triglyceride levels, and increased high-density lipoprotein-cholesterol (HDL-C) levels.14

Rimonabant was approved in Europe but not in the U.S. Anxiety, depression, and suicidal ideation were AEs observed in the RIO trials and in other unpublished trials. Concerns about these effects led to a unanimous vote by the FDA expert panel against marketing the drug. Other pharmaceutical companies followed suit and halted research on their CB1 receptor antagonists. Soon afterward, the European Medicines Agency blocked the marketing of rimonabant, resulting in the temporary suspension of research within this class of drugs.15

Interest in the endocannabinoid system has been revived. New molecules are being studied in hopes of developing a drug similar to that of exenatide (Byetta, Amylin/Eli Lilly), which is used in diabetes. Liraglutide increases insulin secretion in the presence of elevated blood glucose levels, reduces glucagon secretion, increases B-cell replication, and decreases the desire for food intake. Liraglutide is indicated for the treatment of type-2 diabetes, but its usefulness in treating obesity has been studied following the effects it exhibits on weight loss. In an open-label trial of 464 patients that compared exenatide and liraglutide in type-2 diabetes, weight loss for the two drugs was comparable over a period of 28 weeks. Patients receiving liraglutide 1.8 mg daily lost an average of 3.24 kg from baseline; those receiving exenatide 10 mcg twice daily lost an average of 2.87 kg from baseline. The difference between the two groups was not statistically significant (P = 0.2235).18

When GLP-1 receptors are stimulated within the brain, appetite and subsequent food intake normally decrease.19 However, it is not clear whether the weight loss occurs primarily through liraglutide’s action on the GLP-1 receptors or if it is secondary to the drug’s AEs, which include nausea, vomiting, and diarrhea in approximately 25% of individuals taking this medication.20

A 20-week trial was conducted to evaluate the effects of liraglutide on weight loss in 564 nonobese patients from 19 sites in Europe. Participants received liraglutide 1.2 mg, 1.8 mg, 2.4 mg, or 3 mg or placebo once daily or orlistat 120 mg three times daily. Results were promising; the liraglutide patients lost 4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg, respectively, compared with a loss of 2.8 kg with placebo and 4.1 kg with orlistat. Also of note, more than 75% of patients lost 5% or more of their body weight with the highest dose of liraglutide, compared with 30% of the placebo patients. However, nausea and vomiting were seen as major side effects, leading some patients to withdraw from the study.

The 2.4-mg and 3-mg doses, which provided the greatest weight loss, are higher than the current dose used in the treatment of diabetes (1.8 mg daily). Additional benefits seen in patients who received liraglutide included decreases in waist circumference, blood pressure, and the incidence of prediabetes.21 In addition to the drug’s gastrointestinal (GI) disturbances, liraglutide must be given subcutaneously, which may be a deterrent for many patients.

Serotonergic Drugs

For many years, it has been known that the serotonin system affects satiety and eating behaviors. Several drugs that incorporate this system have been developed in order to produce weight loss. Amphetamines and their derivatives, weak serotonin reuptake inhibitors (SRIs), have been used to decrease appetite, although their major mechanism of action contributes to their effects on norepinephrine.

Later in the 20th century, other SRIs were developed, including fenfluramine (e.g., Ponderax and Adilax); dexfenfluramine (Redux, Interneuron); and sibutramine, which superseded it. Dexfenfluramine was removed from the market in 1997 because of its potential to damage heart valves. Although sibutramine was initially considered a safer alternative than both dexfenfluramine and fenfluramine, it was removed from the U.S. market in 2010.

Researchers have speculated that agonism of 5-hydroxy-

continued on page 287
treatment of Parkinson’s disease and Alzheimer’s disease; however, results were not promising for these disease states.

In addition to the weight loss, a decreased waist circumference and improved lipid profiles were noted with tesofensine.²⁵ Long-term safety trials of the medication are under way, but modifications are expected because the comparator arm in the earlier trial was receiving sibutramine. In November 2010, NeuroSearch announced that it would be seeking a partner to help develop tesofensine.

Cetilistat (ATL-962)

Cetilistat (Norgina BV/Alizyme) is a novel inhibitor of gastrointestinal (GI) and pancreatic lipases. Its mechanism of action mimics that of orlistat (Xenical) by preventing absorption of approximately one-third the amount of fat consumed. Because these drugs have their effect primarily within the GI system, side effects are limited to this system.

In an initial trial comparing cetilistat with orlistat, patients were given placebo, cetilistat 40 mg three times daily, cetilistat 80 mg three times daily, cetilistat 120 mg three times daily, or orlistat 120 mg three times daily. During the 12-week trial, the groups receiving cetilistat, compared with placebo subjects, lost significantly more weight as follows: 80 mg, 3.85 kg \( (P = 0.01) \); 120 mg, 4.32 kg \( (P = 0.0002) \); and orlistat, 3.78 kg \( (P = 0.008) \).

Both cetilistat and orlistat also benefited patients with diabetes, as evidenced by a significant decrease in HbA1c over placebo, as follows: cetilistat, 80 mg \( (P = 0.018) \); 120 mg \( (P = 0.015) \); and orlistat \( (P = 0.04) \). The difference between cetilistat and orlistat was in both the severity and the number of GI side effects. This is very important, because orlistat is often poorly tolerated and may need to be discontinued because of the embarrassing and troublesome effects that can occur, including oily fecal discharge, flatulence, and even fecal incontinence.

Although the overall number of patients reporting these AEs was similar in both groups, more events (541) were reported with orlistat, compared with 428 events reported for cetilistat 120 mg \( (P = 0.0148) \). Patients also reported more severe events with orlistat (55) compared with cetilistat (31) \( (P = 0.0546) \).²⁶ Phase 3 trials are currently in progress in Japan.

Combination Drugs

For many years, the importance of combination therapy in the treatment of obesity has been recognized. Previous combinations that are no longer used include caffeine/ephedrine and phenetermine/flunuramine (Phen-Fen). When either caffeine or ephedrine was used alone, studies were unable to produce effective maintained weight loss, but when they were combined, modest sustainable weight loss was observed with

Lorcaserin (Lorcress)

The unapproved compound that came closest to being brought to market was lorcaserin (Lorcress, APD-356), a selective 5-HT₅₆ agonist developed by Arena Pharmaceuticals. In a large, multicenter trial, involving 3,182 patients, lorcaserin was studied for its effects on weight loss in the Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) trial. Patients received either lorcaserin 10 mg twice daily or placebo for 52 weeks, followed by either placebo or lorcaserin for one more year. Lifestyle modifications and counseling were provided to all participants. The primary endpoints were weight loss at one year and maintenance of weight loss at two years.

Patients in the lorcaserin arm lost an average of 5.8 kg, compared with 2.2 kg in the placebo arm \( (P < 0.001) \). A greater percentage of participants who continued with lorcaserin after the initial 52 weeks were more likely to maintain that weight loss (68%) than patients who received placebo (50%) \( (P < 0.001) \). At one year, valvulopathy did not occur with statistical significance in the lorcaserin group (2.7%) compared with the placebo group (2.3%) \( (P = 0.70) \). This trend continued for two years (2.6%, lorcaserin; 2.7%, placebo).

Psychiatric AEs, such as depressive episodes, also resulted in little difference between lorcaserin (2.5%) and placebo (2.2%). The most frequently reported AEs were headache, upper respiratory infection, nausea, nasopharyngitis, and dizziness.²³

In October 2010, lorcaserin was denied a New Drug Application based on data related to drug-emergent mammary adenocarcinoma observed in rats, as well as an unidentified mode of action and unclear safety margin for drug-emergent brain astrocytoma. In December 2010, Arena indicated that it would continue to try to gain approval, and in January 2011, the company stated that it expects to resubmit the NDA by the end of 2011.

Tesofensine (NS-2330)

Tesofensine (NeuroSearch A/S) is derived from the phenyltropane family of drugs. It exhibits its effects through the inhibition of serotonin, norepinephrine, and dopamine reuptake.²⁴ The agent was first studied as a potential drug for the treatment of Parkinson’s disease and Alzheimer’s disease; however, results were not promising for these disease states. One notable side effect was the weight reduction observed in those who received the drug.

An initial phase 2 trial enrolling 161 treated volunteers showed significant differences in weight compared with placebo patients after 24 weeks. Participants who received placebo and lifestyle modifications lost an average of 2% of their body weight; by contrast, the tesofensine subjects lost 4.5% of their body weight with 0.25 mg daily, 9.2% with 0.5 mg daily, and 10.6% with 1 mg daily.

Common AEs included nausea, constipation, and dry mouth. With regard to psychiatric AEs, anxiety and depression were not significantly greater in the tesofensine patients; however, confusion and sleep disturbances were noted. As a result of tesofensine’s mechanism of action, elevations in blood pressure and pulse rate were observed. The increase in blood pressure was not statistically significant, but statistical significance over placebo was reached in heart rates with both 0.5 mg and 1 mg, for an increase of 7.8 and 8.5 beats/minute, respectively, with tesofensine and 0.4 beats/minute with placebo.

In addition to the weight loss, a decreased waist circumference and improved lipid profiles were noted with tesofensine.²⁵ Long-term safety trials of the medication are under way, but modifications are expected because the comparator arm in the earlier trial was receiving sibutramine. In November 2010, NeuroSearch announced that it would be seeking a partner to help develop tesofensine.
these two formerly available over-the-counter products. Current therapies have been unable to compete with the phen-fen combination, in which patients were able to lose up to 15% of their body weight.27

The thought process behind targeting two different mechanisms of action at potentially lower doses, thereby producing fewer AEs, has been quite successful in various disease states. The combination methodology is becoming more common in obesity research as the investigation for a panacea continues.

**Pramlintide (Symlin)/Metreleptin**

Leptin was studied for many years in hopes of finding a blockbuster weight-loss drug. A neurohormone that is produced by fat cells, leptin is used in the regulation of appetite. Individuals who are leptin-deficient experience extreme hyperphagia and are subsequently found to be obese.28 Animals and leptin-deficient humans lose body fat when leptin is administered.29,30 However, when leptin is given to obese individuals who are not leptin-deficient, the results for weight loss have been less than promising,31 possibly stemming from the theory that obese individuals might be leptin-resistant.32 Studies of leptin monotherapy for the treatment of obesity have been stopped.

Along with insulin, amylin (islet amyloid polypeptide) is a hormone that is secreted from the pancreas; it exhibits effects on glucose regulation and energy balance. Pramlintide acetate (Symlin, Amylin Pharmaceuticals), an analogue of amylin that is approved by the FDA for the treatment of diabetes, can cause significant weight loss of approximately 8% when it is given alone.33

Researchers proposed that by combining amylin with leptin, the leptin resistance observed in obese individuals might be reversed.34 They tested this theory in clinical trials by administering metreleptin (methionyl recombinant leptin) and pramlintide to obese individuals. In this study, 177 subjects started a four-week lead-in period with pramlintide at a dose of 180 mcg twice daily for two weeks, followed by 360 mcg twice daily for two more weeks along with concomitant caloric restriction. Participants who lost at least 2% of their body weight were randomly assigned to receive metreleptin 5 mg twice daily, pramlintide 360 mcg twice daily, or metreleptin/pramlintide 5 mg/360 mcg twice daily. After 20 weeks, participants in the combination group lost significantly more body weight than those taking either compound alone (12.9% vs. 8.2% [P < 0.001] and 8.4% [P < 0.01]), respectively. Because the combination is given as an injection, the most common side effect noted, besides nausea, was irritation at the injection site.35 This route of administration may be a consideration if the drug is brought to market.

As of January 2011, the combination drug, which is given as two separate injections twice daily, was in phase 2B extension trials. In March 2011, however, it was reported that Amylin and Takeda suspended the ongoing phase 2 trial because of the discovery of neutralizing antibodies to leptin.

**Bupropion/Naltrexone (Contrave)**

Pro-opiomelanocortin (POMC) neurons are found in the hypothalamus and are used by the body to determine energy balance and produce anorexia when stimulated. The hormone leptin is believed to stimulate POMC cells and potentially produce an anorexic effect.36 As mentioned previously, however, resistance to leptin may occur.

One drug that stimulates POMC cells and has been used off-label for weight loss is bupropion. Unfortunately, bupropion appears to produce minimal weight loss (less than 5%).37 It has been postulated that when POMC cells are stimulated, a compensatory autoinhibitory feedback mechanism that utilizes endogenous opioids may be triggered, thereby decreasing weight-loss potential. Researchers believe that by inhibiting the feedback mechanism through opioid antagonism with naltrexone, weight loss may be enhanced with bupropion.38 Initial studies of the combination of bupropion/naltrexone were promising,39 and four phase 3 trials were subsequently completed.

The first completed study compared bupropion/naltrexone therapy with both monotherapy and placebo. During this 24 week, randomized, placebo-controlled and monotherapy-controlled, double-blind phase 2 trial, 419 participants were assigned to receive sustained-release (SR) bupropion 400 mg/day, immediate-release (IR) naltrexone 48 mg/day, placebo, or a combination consisting of IR naltrexone at 16, 32, or 48 mg daily, plus bupropion SR 400 mg daily.

Weight loss was statistically significant, compared with monotherapy, for all three combinations (7.1 kg, 6.6 kg, and 6.9 kg, respectively, versus 1.2 kg with placebo, 1.5 kg with naltrexone monotherapy, and 3.1 kg with bupropion monotherapy). An exception was the 48-mg combination therapy versus bupropion monotherapy (P = 0.0684). One interesting outcome of this trial was that the attrition rate was about 40%.37

**COR-I.** The largest trial involving this drug combination, Contrave Obesity Research I (COR-I), has been completed. This phase 3 trial provided data from 1,742 patients enrolled in the study. Patients were given naltrexone SR 32 mg plus bupropion SR 360 mg, naltrexone SR 16 mg plus bupropion SR 360 mg, or placebo for 56 weeks. All participants also began a reduced-calorie diet and a light exercise program.

Weight loss was modest at 6.1% (P < 0.0001) and 5% (P < 0.0001) in the treatment groups, respectively, and at 1.3% in the control group. Overall, 16% of controls lost 5% of body weight or more, compared with 48% of the naltrexone 32-mg/bupropion group (P < 0.0001) and 39% of the naltrexone 16-mg/bupropion group (P < 0.0001).40

**COR II.** This phase 3 trial also has promising findings; patients lost an average of 17.5 pounds (7.5%) with naltrexone SR 32 mg/bupropion SR versus 3.4 pounds (2.5%) with placebo (P < 0.001 vs. placebo). These results were observed in 701 participants after 56 weeks of treatment,41 and their publication is still anticipated. On April 4th, 2011, at the 60th Annual Scientific Session of the American Colleges of Cardiology, Orexigen announced that Contrave did not alter circadian variations in blood pressure. That entire study has yet to be published.

**COR—Diabetes.** Another 56-week multicenter, placebo-controlled, double-blind, randomized trial included 505 overweight or obese patients with type-2 diabetes. HbA1c levels were between 7% and 10%. Patients were assigned, in a 2:1 ratio, to receive naltrexone SR 32 mg/bupropion SR 360 mg (Contrave) or placebo. Twice as many patients lost at least 5% of

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**Treatment Options for Obesity**
their body weight with ContraVe, compared with placebo, on an intent-to-treat basis (44.5% vs. 18.9%, respectively; \(P < 0.001\)), and 44% of ContraVe patients reached their target HbA1c (below 7%), compared with 26% of the placebo patients \((P < 0.001)\).42 COR–BMOD. The 56-week, placebo-controlled, randomized COR–Behavior Modification trial examined the efficacy and safety of naltrexone plus bupropion as an adjunct to intensive behavior modifications. In a 1:3 ratio, 793 participants received either placebo plus behavior modification or naltrexone SR 32 mg daily plus bupropion SR 360 mg daily plus behavior modifications. At week 56, rates of weight loss were 5.1% with placebo and behavioral modifications and 9.3% with the combination drug plus behavior modifications \((P < 0.001)\). Overall, 66.4% of patients in the combination treatment group lost 5% or more of their body weight, compared with 42.5% of the placebo group \((P < 0.001)\).43

Side effects with this combination were relatively minor: headache, constipation, dizziness, vomiting, and dry mouth were the most common complaints. Some secondary beneficial effects were noted, including a decrease in waist circumference, an increase in HDL-C levels, a decrease in triglycerides, and improved insulin resistance. The greatest benefit with this drug may stem from the decrease in cravings that individuals report.

Summary. In February 2011, the FDA rejected ContraVe because of the possibility of increased cardiovascular complications. The FDA has advised the manufacturer to conduct additional studies. It is unclear whether Orexigen Therapeutics Inc., a relatively small pharmaceutical company, will have the funding to complete these additional safety trials.

For more information on ContraVe, please see this month’s Drug Forecast on page 255.

Phentermine/Topiramate (Qnexa) As discussed earlier, phentermine has been used to treat obesity since 1959. Topiramate (Topamax, Ortho-McNeil), an antiepileptic agent, has been used off-label for obesity for many years following the discovery that it produced weight loss in individuals who used this drug. Trials of topiramate alone were halted because of cognitive AEs, including memory impairment.44 In hopes of reducing AEs, the combination of topiramate and phentermine (Qnexa, Vivus) was studied in two phase 3 trials, EQUIP and CONQUER.

EQUIP (OB-302). This 52-week, randomized, double-blind, placebo-controlled, multicenter study enrolled 1,267 participants with an average BMI of 42.1 kg/m². Participants received phentermine 3.75 mg/topiramate 23 mg, phentermine 15 mg/topiramate 92 mg, or placebo once daily. Mean weight loss at 52 weeks in the intent-to-treat group was 5.1%, 11%, and 1.6%, respectively \((P < 0.0001)\) vs. placebo. The number of participants who lost at least 5% of their body weight was also promising—45%, 67%, and 17% in each group, respectively \((P < 0.0001)\) vs. placebo.

CONQUER (OB-303). Another 52-week, randomized, double-blind, placebo-controlled, multicenter trial enrolled 2,487 participants with an average BMI of 36.6 kg/m². Participants received phentermine 3.75 mg/topiramate 23 mg, phentermine 15 mg/topiramate 92 mg, or placebo once daily. Results showed a mean weight loss at 52 weeks in the intent-to-treat group of 8.4%, 10.4%, and 1.8%, respectively \((P < 0.0001)\) vs. placebo. The number of participants who lost at least 5% of their body weight was also promising—62%, 70%, and 21% in each group, respectively \((P < 0.0001)\) vs. placebo.

Secondary endpoints benefiting the combination subjects included reductions in blood pressure (by 6 mm Hg) and triglycerides (by 56 mg/dL). More control patients dropped out of the study, compared with the treatment group, suggesting that tolerability might not be a problem. One concern was cognitive impairment, which did not appear to be significantly greater in the treatment group.45

In July 2010, an FDA advisory panel rejected the New Drug Application for Qnexa based on the concern for memory and concentration issues as well as the potential risk for pregnant women. Safety trials were continued until late October 2010, when Vivus decided to withdraw its New Drug Application.

Zonisamide/Bupropion (Empatic) In clinical trials, an antiepileptic drug, zonisamide (Zonegran, Eisai), was observed to have a side effect of weight loss. The dopaminergic and serotonergic activities of zonisamide are thought to be the mechanism of action behind its usefulness in the treatment of obesity.

An early trial of zonisamide alone showed a 9.4% weight loss in the treated group and a 1.8% loss in the placebo group \((P < 0.001)\),46 prompting additional studies and expanding its off-label usage. Other studies were not as impressive, and an overall meta-analysis estimated weight loss with zonisamide to be 3 kg greater than that with placebo.47

By combining zonisamide with bupropion (Empatic, Orexigen), the researchers hoped to increase efficacy without increasing AEs. A small initial trial of 18 obese women was completed and showed promising results—a weight loss of 7.2 kg with the combination and 2.9 kg with placebo \((P = 0.003)\).48

In the multicenter, double-blind, randomized phase 2 trial that was recently completed,49 729 participants received bupropion SR 360 mg daily, zonisamide 120 mg daily, zonisamide 360 mg daily, bupropion SR 360 mg plus zonisamide 120 mg daily, bupropion SR 360 mg plus zonisamide 360 mg daily, or placebo. Patients receiving bupropion SR 360 mg/zonisamide 360 mg daily lost an average of 7.5% of their body weight; the bupropion SR 360 mg/zonisamide 120 mg daily group lost an average of 6.1%, and the placebo group lost an average of 1.4% \((P < 0.001)\), compared with placebo.

For the patients losing 5% or more of their body weight, 60.4% receiving bupropion SR 360 mg/zonisamide 360 mg daily achieved this goal, whereas 46.9% of participants receiving bupropion SR 360 mg/zonisamide 120 mg daily and 14.7% receiving placebo achieved the threshold \((P < 0.001)\), compared with placebo.

Patients continued to lose weight throughout the trial without showing the plateau effect, often seen with anti-obesity medications. Secondary beneficial effects included a decrease in waist circumference, triglyceride levels, and blood pressure. Adverse events included headache, insomnia, and nausea. Urticaria was also reported in some patients, leading them to discontinue the trial.49 As of this writing, phase 2 trials have been concluded.
CONCLUSION

Obesity is a complex metabolic and behavioral disorder and a leading cause of morbidity and mortality. Drugs targeting metabolic and behavioral components of obesity have been studied, and although they have been modestly effective, they are plagued with unacceptable AEs. The drive to develop new anti-obesity drugs is fueled by the increasing prevalence of obesity coupled with the understanding of new mechanisms in weight regulation. This has led to the pursuit of new agents and the strategy to combine agents approved for other indications.

Anti-obesity medications currently in clinical trials will face several regulatory hurdles. Safety concerns have halted the progression of some treatments and have put pressure on companies to develop safer agents. Information from further studies will raise the question of whether a modest weight reduction will translate into improved morbidity and mortality outcomes. The success of these agents will be linked to reimbursement by third-party payers. To that end, it is unclear whether pharmaceutical companies will change the focus of research to other comorbidities commonly associated with obesity.

There is an enormous unmet need for anti-obesity medications that are safe, effective, and more powerful than those currently available and that would produce fewer AEs. Drugs targeting the central nervous system pathways and gut hormones represent a valuable new target in the development of obesity treatments. If these targeted approaches can overcome regulatory and safety challenges, they will represent encouraging weapons in the treatment of obesity.

REFERENCES


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